Long-Acting Narcotic Analgesics Review

03/15/2007

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Overview

Pain is often undertreated, and pain management greatly misunderstood. Seventy-three percent of hospitalized medical patients receiving opiates were found in severe or moderate distress despite their analgesic regimen.[1] Caregivers' misconceptions regarding opiate doses, duration of analgesic effect, and fear of addiction were reportedly responsible for this undertreatment. Similar problems have been reported in ambulatory patients.[2] Different management techniques are utilized for acute and chronic pain. When properly used, long-acting opioids provide a decrease in administration frequency, longer periods of consistent pain control, and lower the incidence of adverse effects.

Pharmacology

Opioid agonists act primarily through interaction with opioid mu-receptors located in the brain, spinal cord, and smooth muscle. The primary site of therapeutic action is the central nervous system (CNS). Opioid agonists produce respiratory depression by direct action on the brain stem respiratory center.

FDA-approved Indications

Drug	Manufacturer	Schedule	Indication(s)
fentanyl transdermal (Duragesic®)	generic, Janssen	CII	Chronic pain in patients who require continuous opioid analgesia for pain that can not be managed by lesser means (age > 2 years)
methadone (Dolophine®)	generic	CII	Relief of moderate to severe pain Detoxification and maintenance treatment of narcotic addiction
morphine sulfate extended release (Avinza™)	Ligand	CII	Moderate to severe pain requiring opioid therapy for an extended time period
morphine sulfate extended release (Kadian®)	Alpharma	CII	Moderate to severe pain requiring opioid therapy for an extended time period
morphine sulfate extended release (MS Contin®)	generic, Purdue	CII	Moderate to severe pain requiring opioid therapy for an extended time period
morphine sulfate extended release (Oramorph® SR)	generic, Xanodyne	CII	Relief of pain in patients who require opioids for more than a few days
oxycodone controlled release (OxyContin®)	generic, Purdue	CII	Moderate to severe pain
oxymorphone extended release (Opana® ER)	Endo	CII	Moderate to severe pain requiring around-the-clock, continuous opioid for an extended time
tramadol extended release (Ultram® ER)	Ortho-McNeil	Not scheduled	Moderate to moderately severe chronic pain requiring opioid therapy for an extended time period

Pharmacokinetics

Drug	Half-Life (hr)	Tmax (hr)	Excretion
fentanyl transdermal (Duragesic)[3]	17	33.5-38.1	65% metabolized and renally eliminated
methadone (Dolophine)[4]	8-59	1-7.5	primarily metabolized and renally eliminated
morphine sulfate ER (Avinza)[5]	~2	8.6-10.3	90% metabolized and renally eliminated
morphine sulfate ER (Kadian)[6]	2-4	8.6-10.3	90% metabolized and renally eliminated
morphine sulfate ER (MS Contin)[7]	2-4	N/A	90% metabolized and renally eliminated
morphine sulfate ER (Oramorph SR)[8]	2-4	3.6-3.8	90% metabolized and renally eliminated
oxycodone CR (OxyContin)[9]	4.5	1.6-3.2	primarily metabolized and renally eliminated
oxymorphone (Opana ER)[10]	9.4-11.3	N/A	highly metabolized; eliminated in urine and feces
tramadol ER (Ultram ER)[11]	tramadol 7.9 metabolites 8.8	tramadol 12 metabolites 15	30% excreted as tramadol, 60% excreted as active metabolites in the urine

N/A = no data available

Clinical Trials

Search Strategies

Articles were identified through searches performed on PubMed, www.ifpma.org/clinicaltrials, and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled, comparative trials for FDA-approved indications are considered the most relevant in this category. Clinical outcome trials rather than surrogate markers as trial primary outcome parameters are considered the most relevant in this class. Criteria for study inclusion in this review are the following: English language, human studies, analyze the data consistently with the study question, randomly allocate participants to comparison groups, include follow-up (endpoint assessment) at least 80 percent of those entering the investigation, and have clearly stated, predetermined outcome measure of known or probable clinical importance. Studies were determined to be free of bias. Unbiased studies were then reviewed for validity and importance. The majority of clinical drug trials are sponsored and/or funded by pharmaceutical manufacturers. While objective criteria were used to ensure that the studies included are free of bias, the potential influence of manufacturer sponsorship/funding must be considered.

Guidelines for pain management recommend a stepped approach with consideration for the type of pain and response to therapy.[12,13] The initial therapy should include nonopioid analgesics such as NSAIDs. For mild to moderate pain, oral combinations of acetaminophen and NSAIDs with opioids are recommended. Adjunctive therapies, such as tricyclic antidepressants or

corticosteroids, may be added. For moderate to severe pain, opioid analgesics are the mainstay. Titration of dose and frequency should be individualized to the patient's response and experience of side effects.

methadone (Dolophine) versus morphine sulfate SR

A total of 103 patients with pain requiring initiation of strong opioids were randomly assigned to treatment with methadone 7.5 mg every 12 hours and 5 mg every four hours as needed or morphine 15 mg sustained release every 12 hours and 5 mg every four hours as needed.[14] After four weeks, patients receiving methadone had more opioid-related dropouts than those receiving morphine (22 versus six percent; p=0.019). The opioid escalation index at days 14 and 28 were similar between the two groups. More than three-fourths of patients in each group reported a 20 percent or more reduction in pain intensity by day eight; at four weeks, the proportion of patients with a 20 percent or more reduction in pain was similar: 0.49 in the methadone group and 0.56 in the morphine group.

morphine sulfate ER (Avinza) versus morphine sulfate SR (MS Contin) versus placebo

In a four-week randomized, placebo-controlled, double-blind trial, 295 osteoarthritis patients who had previously failed to obtain adequate pain relief with NSAIDs and acetaminophen received one of three treatments: morphine sulfate ER (Avinza) 30 mg once daily, morphine sulfate SR (MS Contin) 15 mg twice daily, or placebo twice daily.[15] Both morphine sulfate ER (Avinza) and morphine sulfate SR (MS Contin) reduced pain and improved several sleep measures versus placebo. Analgesic efficacy was comparable between both morphine sulfate dosage forms. The active treatment groups documented similar occurrences in adverse drug reactions with nausea and constipation being the most common.

oxycodone controlled-release (OxyContin) versus oxycodone immediate release

A multicenter, randomized, double-blind, parallel-group study was performed in 111 patients with cancer pain.[16] Patients were being treated with fixed-combination opioid/nonopioid analgesics at study entry. Patients received 30 mg of oxycodone CR tablets every 12 hours or 15 mg of oxycodone IR four times daily for five days. No titration or supplemental analgesic medications were permitted. The mean baseline pain intensity (0 = none, 1 = slight, 2 = moderate, 3 = severe) was 1.5 for the oxycodone CR-treated group and 1.3 for the group given oxycodone IR (p>0.05). The five-day mean pain intensity was 1.4 and 1.1 for the CR and IR groups, respectively (p>0.05). Discontinuation rates were equivalent (33 percent). There was no significant difference between treatment groups in the incidence of adverse events.

Cancer patients who required therapy for moderate to severe pain were randomized to oxycodone CR every 12 hours (n=81) or oxycodone IR four times daily (n=83) for five days in a multicenter, double-blind study.[17] Rescue medication was allowed. Pain intensity remained slight during the study, with mean oxycodone doses of 114 mg/day for CR and 127 mg/day for IR. Acceptability of therapy was fair to good with both treatments. Discontinuation rates for lack of acceptable pain control were four percent with CR and 19 percent with IR. Fewer adverse events were reported with CR than with IR (p=0.006).

oxymorphone ER (Opana ER) and oxycodone CR (OxyContin)

A multicenter, randomized, double-blind, placebo- and active-controlled trial was conducted to compare the analgesic efficacy and safety of oxymorphone ER with placebo and oxycodone CR in patients with moderate to severe chronic low back pain requiring opioid therapy.[18] Patients

(n=213) were randomized to receive oxymorphone ER (10 to 110 mg) or oxycodone CR (20 to 220 mg) every 12 hours during a seven- to 14-day dose-titration phase. Patients achieving effective analgesia at a stable opioid dose entered an 18-day double-blind treatment phase and either continued opioid therapy or received placebo. With stable dosing throughout the treatment phase, oxymorphone ER (79.4 mg/day) and oxycodone CR (155 mg/day) were superior to placebo for change from baseline in pain intensity as measured on a visual analog scale (p=0.0001). Adverse events for the active drugs were similar; the most frequent were constipation and sedation. Oxymorphone ER was equianalgesic to oxycodone CR at half the milligram daily dosage with comparable safety.

tramadol ER (Ultram ER)

A randomized, double-blind, placebo-controlled, parallel-group, 12-week study evaluated 246 patients with radiographically confirmed OA of the knee meeting the American College of Rheumatology diagnostic criteria.[19] Following a wash-out period, patients were randomized to tramadol ER or placebo. Tramadol ER was initiated at 100 mg daily and increased to 200 mg daily by the end of one week of treatment. After the first week, further increases to tramadol ER 300 mg or 400 mg daily were allowed. The mean tramadol ER dose was 276 mg. On the primary outcome variable of average change from baseline in Arthritis Pain Intensity VAS over 12 weeks, tramadol ER was superior to placebo ($p<0.001$). All efficacy outcome measures statistically significantly favored tramadol ER over placebo.

Pediatrics

Fentanyl transdermal (Duragesic) is approved for use in patients as young as two years of age.

Warnings

Fentanyl transdermal (generic, Duragesic) has a black box warning reminding prescribers that Schedule II opioids have the highest potential for abuse and are associated with the risk of fatal overdoses due to respiratory depression. The warning also discusses using the product only in patients who are already tolerant to opioid therapy. Contraindications include use in patients who are not opioid-tolerant, require opioid analgesia for a short period of time, need analgesia for post-operative pain, or have mild or intermittent pain. Drug interactions are seen with CYP 3A4 inhibitors. The patches are for transdermal use only.

The black box warning for methadone indicates that cardiac and respiratory deaths have been reported during initiation and conversion of pain patients to methadone treatment from other opioid agonists. Cases of QT interval prolongation and serious arrhythmia have also been observed.[20]

The black box warning for morphine sulfate ER (Avinza) states that capsules are to be swallowed whole, and are not to be taken concomitantly with alcohol, which may cause a rapid release of active ingredient.[21] This may cause increased adverse events and even overdose.

Oxycodone ER (generic, OxyContin) has a black box warning that describes the abuse potential of this product.[22] It also states that it is for long-term use, and not as-needed treatment. The tablets are to be swallowed whole, and the 80 and 160 mg tablets are to be used only in opioid-tolerant patients.

Seizures have been reported in patients taking tramadol within the recommended dosage range; use caution in patients taking other neuroleptics such as SSRIs, TCAs, and MAO inhibitors.[23]

Tramadol ER (Ultram ER) should not be prescribed for patients who are suicidal or addiction-prone.

Oxymorphone ER (Opana ER) has an abuse liability similar to that of other opioids, legal or illicit.[24] Oxymorphone ER is to be swallowed whole, not broken, and is not for as-needed use. Concomitant use with alcohol may increase blood levels of oxymorphone and cause a potentially fatal overdose.

Drug Interactions

All agents should be used with caution and in reduced dosage in patients who are concurrently receiving other narcotic analgesics, muscle relaxants, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics, tricyclic antidepressants, and other CNS depressants (including alcohol). Respiratory depression, hypotension, and profound sedation or coma may result.

Monoamine oxidase inhibitors (MAOI) may intensify the actions of other opioids.

Fentanyl, methadone, and tramadol are mainly metabolized by the CYP450 enzyme pathway, so coadministration of these agents with CYP450 enzyme inducers or inhibitors may adversely affect their metabolism.[25,26,27]

*Selected Adverse Effects**

Drug	Asthenia	Constipation	Dizziness	Dyspnea	Headache	Nausea	Rash	Somnolence	Vomiting
fentanyl transdermal (Duragesic)[28]	>10	>10	3-10	3-10	3-10	24	1-3	>10	33
methadone (Dolophine)[29]	--	v	v	v	v	v	v	v	v
morphine sulfate ER (Avinza)[30]	5-10	>10	--	5-10	>10	>10	5-10	>10	>10
morphine sulfate ER (Kadian)[31]	< 3	9	6	< 3	< 3	7	< 3	9	< 3
morphine sulfate ER (MS Contin)[32]	v	v	v	--	v	v	v	v	v
morphine sulfate ER (Oramorph SR)[33]	v	v	v	--	v	v	v	v	v
oxycodone CR (OxyContin)[34]	6	23	13	1-5	7	23	1-5	23	12
oxymorphone ER (Opana ER)[35]	3.9	27.6	17.8	1-10	12.2	33.1	<1	17.2	15.6
tramadol ER (Ultram ER)[36]	3.5-6.5	12.2-29.7	15.9-28.2	<5	<1	15.1-26.2	--	8.2-20.3	5-9.4

*Incidence is reported as a percentage. Data taken from package information and are not meant to be comparative. v = reported

The American Geriatric Society (AGS) guideline, "The Management of Persistent Pain in Older Persons" addresses "opioids of particular concern" in the geriatric population. Among these agents is tramadol.[37] According to these guidelines, tramadol has opioid activity with apparently low abuse potential and is reportedly about as effective and safe as codeine or hydrocodone. However, tramadol has the additional low risk of inducing seizures.

Dosages

Drug	Starting Dose	Titration	Available Strengths
fentanyl transdermal patches (Duragesic)	25 mcg/hr patch changed every three days	For patients on other opioids, calculate their total 24-hour analgesic requirement. Convert this amount to an equivalent analgesic oral morphine dose (see Package Insert Table C). Package Insert Table D displays the recommended initial Duragesic dose based on the total daily oral morphine dose. Dosage increase may occur after every three days by adding up the rescue medication dosage. Initial doses should be reduced in elderly or debilitated patients.	12 mcg/hr 25 mcg/hr 50 mcg/hr 75 mcg/hr 100 mcg/hr
methadone (Dolophine)	2.5 mg to 10 mg every 8 to 12 hours	Adjust dosage according to the severity of pain and patient response. For exceptionally severe pain, or in those tolerant of opioid analgesia, it may be necessary to exceed the usual recommended dosage.	2.5, 5, 10, 40 mg tablets 1, 2, 10 mg/mL oral solutions
morphine sulfate ER capsules (Avinza)	30 mg daily	Titrate 30 mg per day every four days until sufficient pain control is maintained. Swallow capsules whole. Do not crush, chew or dissolve. May sprinkle beads on applesauce.	30 mg 60 mg 90 mg 120 mg
morphine sulfate ER capsules (Kadian)	One capsule every 12 to 24 hours based on previous opioid requirements	Titrate to pain control. Do not exceed upward titration of more than 20 mg every other day. Swallow capsules whole. Do not crush, chew, or dissolve.	20 mg 30 mg 50 mg 60 mg 80 mg 100 mg
morphine sulfate ER tablets (MS Contin)	15 mg every 12 hours	In adjusting dosing regimens, attention should be given to daily dose, degree of opioid tolerance, if any, and general condition and mental status of the patient	15 mg 30 mg 60 mg 100 mg 200 mg
morphine sulfate ER tablets (Oramorph SR)	15 mg every 12 hours	In adjusting dosing regimens, attention should be given to daily dose, degree of opioid tolerance, if any, and general condition and mental status of the patient	15 mg 30 mg 60 mg 100 mg
oxycodone CR tablets (OxyContin)	10 mg every 12 hours	Except for the increase from 10 mg to 20 mg every 12 hours, the total daily oxycodone dose can be increased by 25 to 50 percent at each increase. Patients should be titrated so that they need no more than two supplemental analgesia doses per day. A conversion chart is found in the package insert for patients on other opioid therapy. For elderly, debilitated, and patients with hepatic impairment, the dosage should be reduced by 33-50 percent. For patients with CLcr<60 mL/min, dosage may need to be lowered by up to 50 percent.	10 mg 20 mg 40 mg 80 mg 160 mg (OxyContin only)
oxymorphone ER tablets (Opana ER)	5 mg every 12 hours	Increase by 5 to 10 mg twice a day every three to seven days based on patient pain intensity and adverse drug reactions. Do not break, crush, chew, or dissolve tablets.	5 mg 10 mg 20 mg 40 mg
tramadol ER tablets (Ultram ER)	One tablet daily	Initiate at 100 mg daily, then titrate at 100 mg increments every five days as needed to relief of pain. Do not use in patients with severe renal or hepatic impairment.	100 mg 200 mg 300 mg

Oxymorphone should be given on an empty stomach; maximum concentration and area under the curve were increased 38 percent when given with a high-fat meal.[38] An *in vivo* study with

oxymorphone ER showed that the maximum concentration increased 31 to 70 percent, on average, following concomitant administration with ethanol. Co-administration must be avoided. Administration of oxymorphone ER in elderly patients resulted in plasma levels that were 40 percent higher than those in younger subjects. Bioavailability of oxymorphone may also be increased in patients with hepatic or renal insufficiency. Formal studies have not yet been done.

Summary

Pain of multiple etiologies remains a substantial problem for many patients presenting in the clinical setting.[39] Pain management must be individualized for each of these patients. There are many opioid analgesic products available, differing in specific opioid, dosage form, and duration of action. Many opioid analgesics are available in clinically effective and cost-efficient generic forms.

Fentanyl is available as a transdermal (generic, Duragesic) dosage form. Fentanyl patches are unique in that they are transdermal, thus being particularly useful in patients unable to tolerate oral medications.

Morphine sulfate has been available as a twice daily sustained release dosage form (MS Contin, Oramorph SR) for many years. More recently, once daily controlled-release dosage forms (Avinza, Kadian) have been marketed. Although the ability of these agents to relieve pain is little, if any, better than the twice-daily dosage forms, the once-daily products are preferred by patients.

Like the controlled-release forms of morphine, oxycodone ER (OxyContin) allows for less frequent (12-hour) dosing of an opioid. There are no data to suggest that this agent is any more effective than controlled-release morphine sulfate. Oxycodone ER has a significant potential for abuse and has recently been associated with increases in crime, as well as deaths, due to illicit use.

Methadone may provide an effective alternative in palliative care of most patients with cancer pain referred for poor pain control and/or adverse effects.

Tramadol ER (Ultram ER) provides a once-daily option that is not a controlled substance. Nevertheless, tramadol is an opioid agonist and is subject to abuse. At this time, there are no comparative data with other extended release products.

Oxymorphone ER (Opana ER) is the most recent entry to the market, but has not yet been sufficiently compared to other long-acting opioids.

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